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Multiple Developmental Defects in Mice with Impaired Recruitment of ASC-2 to Nuclear Receptors

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ASC-2, a recently isolated transcriptional coactivator molecule, stimulates transactivation by multiple transcription factors, including nuclear receptors1-5. CO2CN, a potent dominant negative fragment of ASC-2 encompassing the N-terminal LXXLL motif that binds a broad range of nuclear receptors, competitively inhibited the endogenous ASC-2 from binding these receptors without affecting recruitment of other LXXLL-type coactivators such as TRAP220 and SRC-1 *in vivo*. In contrast, CO2CN/m2, in which the LXXLL motif was mutated to LXXAA to abolish the receptor interactions, was inert. Thus, expression of CO2CN and CO2CN/m2 in mice should allow us to distinguish the physiological role of ASC-2 with nuclear receptors from its action with other transcription factors. Interestingly, CO2CN transgenic mice, but not CO2CN/m2 transgenic mice, exhibited a plethora of pathophysiological phenotypes in eye, heart, and many other organs. These results attest to the essentiality of nuclear receptors in a variety of developmental processes and the importance of ASC-2 as a *bona fide* coactivator of nuclear receptors *in vivo*.